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DEVELOPMENTAL BIOLOGY

On the origin of liver regeneration

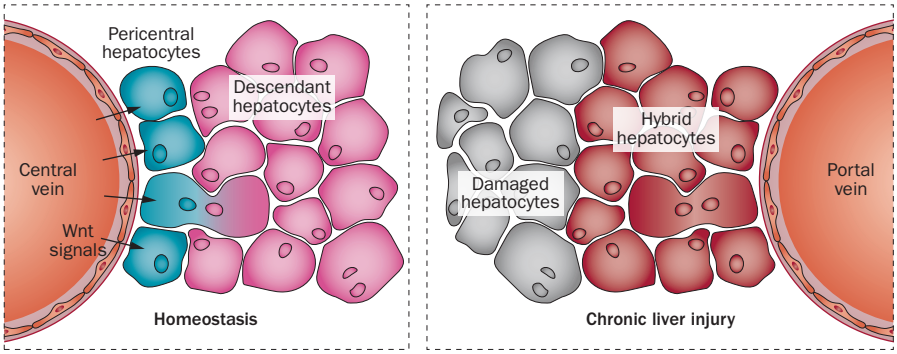
A remarkable feature of the liver is that it can regenerate. This property has been under intense scrutiny as studies have tried to determine the cellular source of liver regeneration. Now, unique populations of cells with the capacity to repopulate the liver have been identified in two new studies. The researchers used similar approaches to identify these cells, but examined the issue in different scenarios—homeostasis and chronic liver injury.

In the first study, published in *Nature,* a unique population of proliferating and self-renewing hepatocytes was identified. These cells were present in a specific niche next to the central vein in the liver lobule, and contributed to liver homeostasis.

As Wnt signalling is crucial to maintain many tissue stem cells, Wang *et al.* performed genetic lineage tracing of Axin2$^+$ cells (a marker of Wnt-responsive cells) in the livers of mice, finding Axin2$^+$ cells located around the central vein. Following the fate of these cells revealed that the Axin2$^+$ pericentral cells generate clones of hepatocytes that expand over time from the central vein to the portal vein. After 1 year, on average, descendants of Axin2$^+$ cells replaced ~30% of the entire liver area, accounting for ~40% of hepatocytes.

Further characterization of these Axin2$^+$ pericentral hepatocytes revealed that they self-renew (a defining property of stem cells), express Tbx3 (an early liver progenitor marker) and are mostly diploid. By contrast, the descendants of these Axin2$^+$ cells mature into polyploid cells after leaving the pericentral niche and no longer express Tbx3. Finally, central vein endothelium was confirmed as a Wnt-producing niche and local source of Wnt signals required for pericentral cell proliferation.

"Our findings fundamentally change the way we think about the basic cell biology of hepatocytes," says first author Bruce Wang. "It means that the liver … is maintained during homeostasis by a stem cell population," he adds, "and that hepatocytes are not equivalent in their proliferative potential, suggesting that hepatocytes are not a single cell type."



Pericentral hepatocytes have stem-like properties and can repopulate the liver during homeostasis (left). By contrast, hybrid hepatocytes can repopulate the liver after injury. Parts of this figure (left) adapted with permission from Nature Publishing Group © Zaret, K. S. *Nature* **524**, 165–166 (2015).

In the second study, published in *Cell*, researchers identified a subpopulation of liver cells in the periportal area, so-called hybrid hepatocytes. These cells did not expand during homeostasis, but proliferated extensively after chronic liver injury, replenishing the liver without giving rise to hepatocellular carcinoma, an important point given that compensatory hepatocyte proliferation has a key role in liver carcinogenesis.

In mice, Font-Burgada *et al.* observed hybrid hepatocytes in the periportal liver area only (comprising 4.53% of all hepatocytes present). These cells had high regenerative capacity and expressed normal levels of Hnf4α but low levels of Sox9 (mixed markers of hepatocytes and bile duct cells) with a unique transcriptome.

Tracking these cells over time demonstrated that hybrid hepatocytes proliferate (extending from the portal vein to the central vein) and repair the liver after damage in several models of chronic liver injury, with the capacity to transdifferentiate into ductal cells after cholestatic liver injury. Moreover, hybrid hepatocytes could be transplanted into mice with severe liver damage, where they clonally expanded across all liver lobules and promoted survival (none of these mice died, whilst 90% of nontransplanted mice and >50% mice transplanted with conventional hepatocytes died).

"Our model of liver regeneration based on hybrid hepatocytes changes substantially the way we have understood how liver regenerates after damage," says first author Joan Font-Burgada. "It was very striking to see how much tissue was generated from this population of cells."

"What is amazing is that you would think a biological problem as to which way hepatocytes migrate (if at all) would be simple to solve, but it has proved problematic," says Malcolm Alison (Queen Mary University of London, UK), who was not involved in the new studies. "To me, these new data [from Wang *et al.*] are really surprising," says Alison adding that some previous evidence from animal and human studies showed that liver cells migrate away from the portal areas to the central vein, as was observed in the Font-Burgada *et al.* study. "Maybe the liver is adaptable having alternative stem cell niches, one acting as a back-up if the other is damaged," he considers.

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Original articles Wang, B. *et al.* Self-renewing diploid Axin2$^+$ cells fuel homeostatic renewal of the liver. *Nature* **524**, 180–185 (2015) | Font-Burgada, J. *et al.* Hybrid periportal hepatocytes regenerate the injured liver without giving rise to cancer. *Cell* **162**, 766–779 (2015)